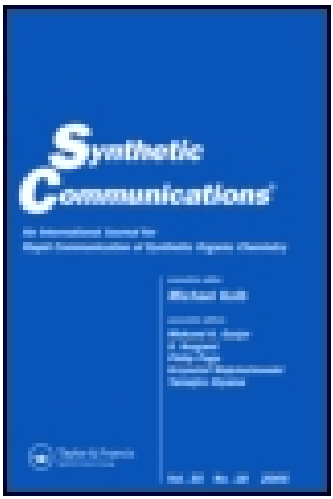

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THE REACTION OF AMIDOXIMES WITH CHLOROACETYL CHLORIDE

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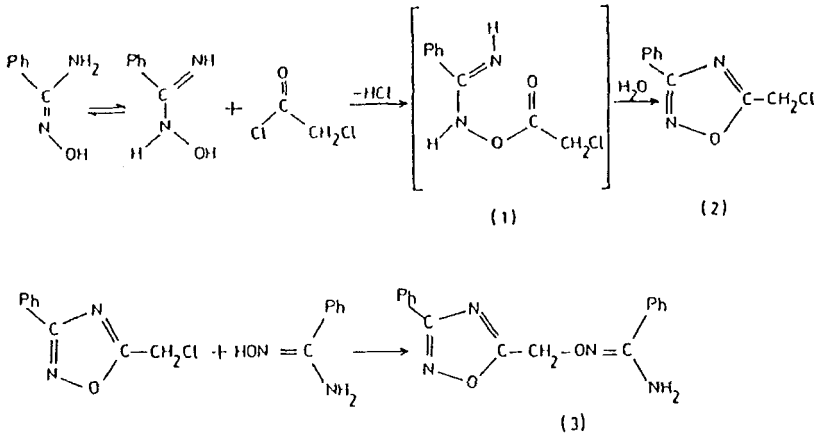
ABSTRACT: 1,2,4-Oxadiazole and 1,2,4-oxadiazine derivatives were obtained from the reaction of amidoximes with chloroacetyl chloride. The treatment of 3,4-disubstituted -Δ^2- dihydro-1,2,4-oxadiazine-5-ones with P_2S_5 gave corresponding 5-thiones.

Five-membered heterocyclic compounds have been synthesized from the reaction of amidoximes with alkylchloroformates[1-3], aldehydes[4], thiophosgene[5,6] and chlorocarbonylsulfenylchloride (CCSC)[7]. Therefore, our attention has been directed to a reaction of amidoximes with chloroacetylchloride for the syntheses of six-membered heterocyclic compounds. The results and possible mechanisms are discussed below.

The reaction of benzamidoxime with chloroacetyl chloride gave 3-phenyl-1,2,4-oxadiazole-5-yl-methyl-O-



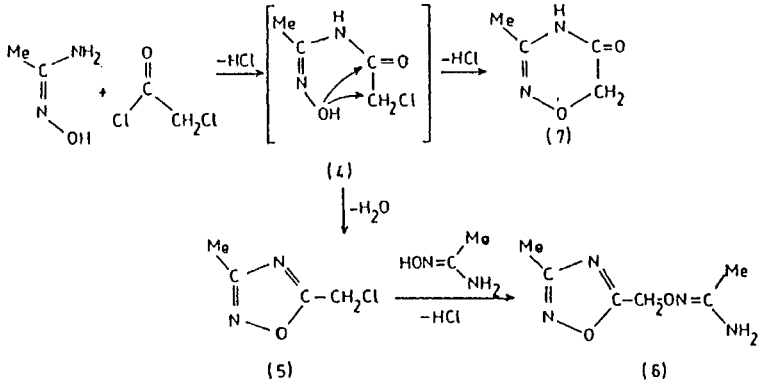
Scheme 1

benzamidoxime via the 3-phenyl-1,2,4-oxadiazole-5-yl-methyl chloride which was also isolated from this reaction. The mechanism of the reaction probably follows the scheme 1.

Here, hydroxyl oxygen of the tautomeric state of benzamidoxime attacks carbonyl carbon of chloroacetylchloride and forms intermediate (1). This can lose water to give compound (2). Then, the reaction of compound (2) with benzamidoxime gives compound (3).

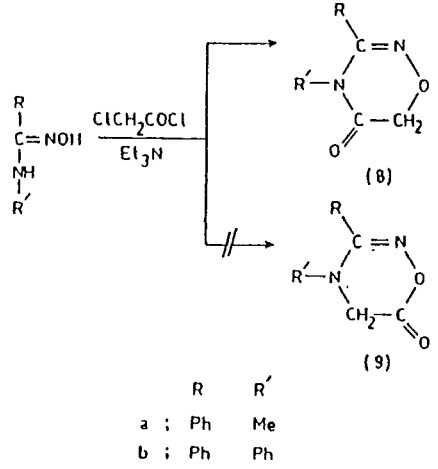
In contrast, the reaction of acetamidoxime with chloroacetylchloride gave 3-methyl-4H-1,2,4-oxadiazine-5(6H)-one (7) along with 3-methyl-1,2,4-oxadiazole-5-yl-methyl-O-acetamidoxime (6) which should be formed via the 3-methyl-1,2,4-oxadiazole-5-yl-methyl chloride (5). The reaction may proceed as below (Scheme 2)

Here, nitrogen atom of $-NH_2$ group of acetamidoxime attacks carbonyl carbon of chloroacetylchloride and gives intermediate (4). Elimination of hydrogen chloride and water from the intermediate (4) gives compound (5) and compound (7). Then, the reaction of compound (5) with acetamidoxime forms compound (6).



Scheme 2

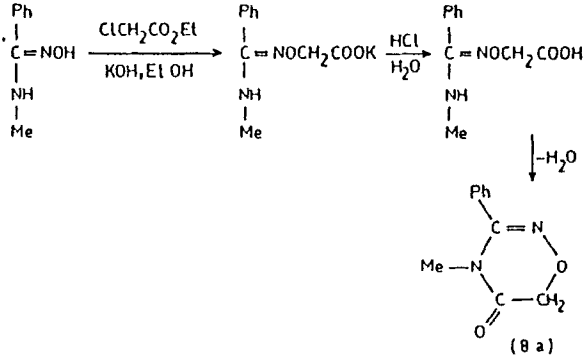
The reaction of N-methylbenzamidoxime and N-phenylbenzamidoxime with chloroacetylchloride in the presence of a hydrogen chloride acceptor gave only 3-phenyl-4-methyl -Δ^2- dihydro-1,2,4-oxadiazine-5-one (8a) and 3,4-diphenyl -Δ^2- dihydro-1,2,4-oxadiazine-5-one (8b) respectively, but did not give 3-phenyl-4-methyl -Δ^2- dihydro-1,2,4-oxadiazine-6-one (9a) or 3,4-diphenyl -Δ^2- dihydro-1,2,4-oxadiazine-6-one (9b) (Scheme 3).



Scheme 3

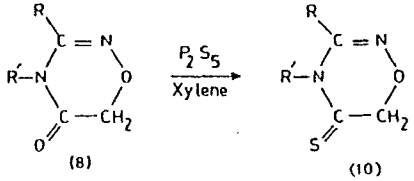
This implies that the nucleophilic attack on carbonyl carbon by nitrogen atom of -NHR' group was dominant in the reaction.

Compound (8a) was also obtained from the reaction of N-methylbenzamidoxime with ethylchloroacetate (Scheme 4



Scheme 4

The treatment of compounds (8a) and (8b) with P_2S_5 gave 3-phenyl-4-methyl -Δ^2- dihydro-1,2,4-oxadiazine-5-thione (10a) and 3,4-diphenyl -Δ^2-dihydro-1,2,4-oxadiazine-5-thione (10b) (Scheme 5).



	R	R'
a ;	Ph	Me
b ,	Ph	Ph

Scheme 5

EXPERIMENTAL

IR spectra: Perkin-Elmer Model 177.-^{1}H-NMR spectra: Bruker Spectrospin (200 MHz). Microanalyses of the compounds were performed at Analytische Laboratorien (Elbach), Germany.

3-Phenyl-1,2,4-oxadiazole-5-yl-methyl chloride (2). A solution of chloroacetylchloride (0.813 g, 7.2 mmol) in benzene (10 mol) was added dropwise to a solution of benzamidoxime (2.448 g, 18 mmol) in benzene (100 ml). An immediate precipitation was observed. Reaction mixture was refluxed for 5 h. After cooling, the white precipitate (benzamidoxime hydrochloride) was filtered off. Solvent was evaporated under reduced pressure at 40°C. Residue was extracted with hot light-petroleum (50-70°C) (3x100 ml). Crude product was recrystallized from light-petroleum (50-70°C) to give compound (2) (1.85 g, 52 %); m.p.39-40°C; -IR (KBr): 1598 cm^{-1} (C=N); -^{1}H-NMR($CDCL_3$):δ4.72 (s, 2H, CH_2Cl), 7.50 (m,3 aromatic H) and 8.10 (m, 2 aromatic H).

$C_9H_7N_2OCl$(194.6) Calcd. C 55.54 H 3.62 N 14.39
Found C 55.47 H 3.67 N 14.63

3-Phenyl-1,2,4-oxadiazole-5-yl-methyl-O-benzamidoxime (3). After the extraction of the compound (2) from the above reaction mixture, the remaining residue was extracted with warm ether(3x100 ml). Crude product was recrystallized from ether-light petroleum (50-70°C) (1:2) to give compound (3) (0.21 g 4%); m.p. 96-97°C; -IR(KBr): 3400, 3300 and 3200 (NH_2), 1625 cm^{-1} (C=N); -^{1}H-NMR ($CDCl_3$):δ 4.90 (s, broad, 2H, NH_2), 5.54 (s, 2H,-CH_2O), 7.70 (m, 8 aromatic H) and 8.06 (m, 2 aromatic H).

$C_9H_8N_2O_2$(294.3) Calcd. C 65.30 H 4.76 N 19.04
Found C 65.31 H 4.88 N 18.91

3-Methyl-1,2,4-oxadiazole-5-yl-methyl-O-acetamidoxime (6). A solution of chloroacetylchloride (1.75 g, 15.5 mmol) in chloroform (20 ml) was added dropwise to a solution of acetamidoxime (3.0 g, 40 mmol) in warm chloroform (300 ml). An immediate precipitation was observed. Reaction mixture was refluxed for 6 h. Precipitate (acetamidoxime hydrochloride) was filtered off and solvent was evaporated under reduced pressure at room temperature. Remaining oily product was extracted with light petroleum (50-70°C) (3x100 ml). Crude product was recrystallized from light petroleum (50-70°C) to give compound (6) (0,28 g, 4%); m.p.59-60°C;-IR(KBr): 3420, 3320 and 3200 (NH_2), 1650 and 1585 cm^{-1}(C=N); -^{1}H-NMR ($CDCl_3$):δ1.82 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.62 (s, broad, 2H, NH_2), 5.12 (s, 2H, NCH_2O).

$C_6H_{10}N_4O_2$(170.1) Calcd. C 42.35 H 5.88 N 32.94
Found C 42.51 H 5.85 N 32.78

3-Methyl-4H-1,2,4-oxadiazine-5(6H)-one (7). After the extraction of the compound (6) from the above reaction mixture the remaining residue was extracted with warm ether (3x100 ml). Crude product was recrystallized from ether-light petroleum (50-70°C) (1:2) to give compound (7) (0.38 g, 8%); m.p.144-145°C; -IR(KBr): 3220, 3080 (NH), 1710 (C=O) and 1630 cm^{-1} (C=N);-^{1}H-NMR ($CDCl_3$):δ2.08 (s, 3H, CH_3), 4.28 (s, 2H, OCH_2) and 9.0 (s, broad, 1H, NH).

$C_4H_6N_2O_2$(114.1) Calcd. C 42.10 H 5.30 N 24.54
Found C 42.31 H 5.48 N 24.28

3-Phenyl-4-methyl-Δ^2-dihydro-1,2,4-oxadiazine-5-one(8a)

Method A

A solution of chloroacetylchloride (0.376 g, 3.3 mmol) in chloroform (5 ml) was added dropwise to an

ice-cooled solution of N-methylbenzamidoxime (0.50 g, 3.3 mmol) and triethylamine (0,673 g, 6.6 mmol) in chloroform (15 ml). The reaction mixture was stirred for 4 days at room temperature. Solvent was evaporated under reduced pressure. The remaining solid material was extracted with acetone. The solvent was evaporated and the crude product was recrystallized from ether-light petroleum (50-70°C) (1:2) to give compound (8a) (0.5 g, 79%); m.p.96-97°C; -IR(KBr): 1710 (C=O), 1600 and 1575 cm^{-1} (C=N); $-^1H$-NMR ($CDCl_3$):δ 3.07 (s, 3H, CH_3), 4.47 (s, 2H, CH_2), and 7.50 (s, 5 aromatic H).

$C_{10}H_{10}N_2O_2$(190.2) Calcd. C 63.14 H 5.30 N 14.72
Found C 63.01 H 5.70 N 15.12

Method B

A solution of potassium hydroxide (1.13 g, 20 mmol) in ethanol (10 ml) was added to a solution of N-methylbenzamidoxime (1.51 g, 10 mmol) and ethylchloroacetate (1.225 g, 10 mmol) in ethanol (10 ml). Reaction mixture was refluxed on a water bath for 5 h. Solvent was evaporated under reduced pressure at 40°C. The residual solid was extracted with hot water. Water was evaporated to dryness. The remaining solid was dissolved in ethanol (20 ml) and filtered. After the evaporation of ethanol the residue was dissolved in water (10 ml), and a conc. HCl solution was added. Then solvent was evaporated to dryness. The oily residue was extracted with ethanol, and solvent was evaporated under reduced pressure. Remaining red solid was heated at 120°-140°C for 3 h. Crude product was recrystallized from cyclohexane to give compound (8a) (0.36 g, 30%); m.p.96-97°C. The compound was found to be identical in all respects with the compound obtained in Method A.

3,4-Diphenyl -Δ^2- dihydro-1,2,4-oxadiazine-5-one(8b). A solution of chloroacetylchloride (0.532 g, 4.7 mmol) in benzene (5 ml) was added dropwise to an ice-cooled solution of N-phenylbenzamidoxime (1.0 g, 4.7 mmol) and triethylamine (0.95 g, 9.4 mmol) in benzene (45 ml). An immediate precipitation was observed. Reaction mixture was stirred for 4 days at room temperature. Precipitate (triethylamine hydrochloride) was filtered off. Benzene was evaporated under reduced pressure at 40°C. Remaining crude product was recrystallized from cyclohexane to give compound (8b) (0.50 g, 42%); m.p.140-141°C; -IR(KBr): 1715 (C=O), 1595 and 1590 cm^{-1} (C=N); -^{1}H-NMR ($CDCl_3$):δ 4.62 (s, 2H, CH_2) and 7.28 (m, 10 aromatic H).

$C_{15}H_{12}N_2O_2$(252.2) Calcd. C 71.41 H 4.79 N 11.10
Found C 71.08 H 5.04 N 10.73

3-Phenyl-4-methyl -Δ^2- dihydro-1,2,4-oxadiazine-5-thione (10a): 3-Phenyl-4-methyl -Δ^2-dihydro-1,2,4-oxadiazine-5-one (8a) (0.445 g, 2.3 mmol) was refluxed with P_2S_5 (0.20 g, 0.90 mmol) in xylene (35 ml) for 11 h. Xylene was evaporated under reduced pressure at 65°C. Residual yellow solid was recrystallized from light petroleum (40-60°C) to give compound (10a) (0.30 g, 62%); m.p.141-142°C; -IR(KBr): 1580 and 1560 (C=N), 1485, 1265 and 1115 cm^{-1} (C=S); -^{1}H-NMR ($CDCl_3$):δ 3.40 (s, 3H, CH_3), 4.70 (s, 2, CH_2) and 7.54 (s, 5 aromatic H).

$C_{10}H_{10}N_2OS$(206.2) Calcd. C 58.23 H 4.79 N 13.58
Found C 58.23 H 5.09 N 13.21

3,4-Diphenyl -Δ^2-dihydro-1,2,4-oxadiazine-5-thione (10b): 3,4-Diphenyl -Δ^2- dihydro-1,2,4-oxadiazine-5-one (8b) (0.335 g, 1.3 mmol) and P_2S_5 (0.115 g, 0.5 mmol) was refluxed in xylene (30 ml) for 10 h.Hot reaction mixture was filtered. Xylene was evaporated under

reduced pressure at 65°C. Residual yellow solid matter was recrystallized from light petroleum (50-70°C) to give compound (10b) (0.15 g, 43%); m.p.113-115°C; - IR(KBr): 1600, 1580 (C=N), 1485, 1260 and 1090 cm^{-1}(C=S); -^{1}H-NMR ($CDCl_3$):δ 4.83 (s, 2H, CH_2) and 7.25 (m, 10 aromatic H).

$C_{15}H_{12}N_2OS$(268.3) Calcd. C 67.14 H 4.50 N 10.43
Found C 67.43 H 4.74 N 10.41

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